

V2 Receptor Antagonist; Tolvaptan

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Hyponatremia is the most common electrolyte disorder in hospitalized patients. Many studies documented that it was related to increased morbidity and mortality in patients with congestive heart failure, liver cirrhosis, and neurologic diseases. Although knowledge of hyponatremia has been cumulated, the optimal management of hyponatremia remains incompletely established in clinical practice because of the diversity of underlying disease states, and its multiple causes with differing pathophysiologic mechanisms. Since vasopressin receptor antagonists have unique aquaretic effect to selectively increase electrolytes-free water excretion, clinicians could apply a more effective method to treat hyponatremia. Tolvaptan has significant evidence that it improves serum sodium levels in patients with euvolemic or hypervolemic hyponatremia related with heart failure, cirrhosis or syndrome of inappropriate anti-diuretic hormone. Tolvaptan has acceptable safety and tolerability for long-term usage in chronic hyponatremia, and the beneficial effects on serum Na⁺ occurred in patients with both mild and marked hyponatremia.

Key Words: tolvaptan; hyponatremia; arginine vasopressin receptors

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Introduction

Hyponatremia is the most common electrolyte disorder in hospitalized patients^{1,2}. Many studies documented that it is related to increased morbidity and mortality in patients with congestive heart failure, liver cirrhosis, and neurologic diseases³⁻⁶. Although knowledge of hyponatremia has accumulated, the optimal management of hyponatremia remains incomplete in clinical practice because of the diversity of underlying disease states, and its multiple causes with differing pathophysiologic mechanisms. Since vasopressin receptor antagonists have unique aquaretic effect to selectively increase electrolytes-free water excretion, clinicians could apply a more effective method to treat hyponatremia.

The vaptans are non-peptide arginine-vasopressin-

receptor antagonists that are orally and intravenously active. Orally active vaptans, compared to intravenous use, are more convenient and similarly effective. This article reviews the various types and functions of vasopressin receptors and the therapeutic role of tolvaptan in clinical conditions.

Arginine Vasopressin (AVP)

AVP is a neuropeptide hormone synthesized in the paraventricular nuclei and supraoptic nuclei of the hypothalamus, and stored in the posterior pituitary⁷. Normally, its secretion is strongly influenced by small changes, as little as 1%, in plasma osmolality detected by osmoreceptors in the hypothalamus⁷. Thus, this process results in fine control of serum sodium levels and serum osmolality⁷. Also, AVP

release is stimulated by a decrease in blood volume through baroreceptors in the carotid artery, aortic arch and left atrium, which sense changes in intra-arterial plasma volume. AVP levels were unsuitably increased in several clinical settings, such as heart failure, liver cirrhosis, syndrome of inappropriate anti-diuretic hormone (SIADH), and surgical stress⁸.

Arginine Vasopressin Receptors

1. V_{1a} Receptors

Vascular smooth muscle cells (in the myocardium), hepatocytes and platelets have V_{1a} receptors that are activated by AVP or agonists, and lead to vasoconstriction in the coronary, peripheral circulation, and platelet aggregation⁹. Also, activated V_{1a} receptors cause an increase in intracellular calcium levels in cardiac myocytes and protein synthesis. V_{1a} receptors are activated by a phosphoinositol signaling pathway.

2. V_{1b} Receptors

V_{1b} receptors are found in the anterior pituitary and have functions related to adrenocorticotrophic hormone release¹⁰. However the role of these receptors has not been found, yet. The V_{1b} receptors, like the V_{1a} receptors, use a phosphoinositol signaling pathway¹⁰.

3. V₂ Receptors

The V₂ receptors are located on the collecting tubules of the kidney and have functions related to free water absorption by activating the aquaporin-2 channel on the apical plasma membrane of the collecting duct cells¹¹. Such antidiuretic function occurs through the adenylate cyclase signaling pathway with intracellular cyclic adenosine monophosphate as a second messenger, in the collecting duct cells^{9,11}.

Vasopressin Receptor Antagonists (VRAs)

Although AVP receptor antagonists were the first developed peptide antagonists in the 1960s and although animal studies showed that these peptides had an anti-diuretic effect, several limitations of clinical use were found. These peptides mediate a paradoxical weak agonism to the V₂ receptor and were seen in human studies to have poor oral bioavailability and short biological half lives⁹.

In 1992, the non-peptide V₂ antagonist was first developed by Yamamura et al¹². These non-peptide VRAs had more bioavailability and longer half lives than the peptide types. Several non-peptide VRAs, including conivaptan, tolvaptan, lixivaptan, relcovaptan (SR-49059) and satavaptan, have been studied in human clinical trials which could be administered through oral or intravenous route and were all derived from benzazepine or oxindole derivatives. They have relatively different selectivity for the various AVP receptor subtypes.

Tolvaptan

Tolvaptan is an orally active, non-peptide, selective V₂ receptor antagonist¹³. It has about 2 times greater affinity for the V₂ receptor than native AVP and a 29-fold greater selectivity for the V₂ receptors than the V_{1a} receptors^{13,14}. It is not related to V_{1b} receptors and also its metabolites have no activity at the V₂ receptor¹³. The effect of tolvaptan is to increase urine free water excretion causing decreased urine osmolality, and increased Na⁺ concentration.

1. Pharmacokinetics

Following oral administration of tolvaptan, at least 40% of an oral dose is absorbed; highly protein bound (99%), and reaches peak concentrations in 2 to 4 hours without any effects from food¹³. Its terminal phase half-life is 12 hours. CYP450 isoenzyme plays a role in its metabolism and its elimination is mainly non-renal. Moderate-to-severe hepatic impairment or congestive heart failure decreases the clearance and

increases the volume of distribution, respectively¹³⁻¹⁵). Patients with chronic kidney disease (creatinine clearance < 10 mL/min) and dialysis were not studied. The onset of free water diuresis and serum Na⁺ increase is about 2 to 4 hours after administration, in addition to the peak effect for diuresis and serum Na⁺, which is within 4 to 8 hours. At 24 hours, about 60% of the peak effect on Na⁺ is maintained. Doses >60 mg/day do not increase the peak effect¹³⁻¹⁵).

2. Clinical Trials

Tolvaptan was evaluated in 2 identical multicenter, randomized, double-blinded, placebo-controlled studies enrolling 448 patients with euvolemic or hypervolemic hyponatremia, as titled, Study of Ascending Levels of Tolvaptan in Hyponatremia (SALT-1 and -2)¹⁶). In SALT-1 and -2 studies, patients were randomly assigned to receive tolvaptan at 15 mg for 30 days once daily titrated up to 60 mg if needed, or placebo for 30 days once daily. Eligible patients were 18 years and older with euvolemic and hypervolemic hyponatremia (defined as a serum Na⁺ < 135 mEq/L) of congestive heart failure, liver cirrhosis, and SIADH. Ineligible diseases and conditions of patients were hypovolemic hyponatremia, psychogenic polydipsia, head trauma, postoperative conditions, uncontrolled hypothyroidism, adrenal insufficiency, and medication-induced hyponatremia were excluded. Other exclusion criteria included the presence of ventricular arrhythmias, systolic blood pressure < 90 mmHg, serum creatinine > 3.5, Child-Pugh score > 10, serum Na⁺ < 120 mEq/L, uncontrolled diabetes, or other neurologic diseases. Patients were allowed to continue conventional therapy of heart failure (even diuretics), and if the Na⁺ rose > 145 or > 12 mEq/L within 24 hours, the next dose of tolvaptan was stopped or decreased, or the investigators allowed the subjects to increase fluid intake. The increase in the average daily area under the curve (AUC) for the Na⁺ concentration was significantly higher in the tolvaptan group than in the placebo group from baseline to study day 4, and day 30 (*P* < 0.001). In subgroup analysis categorized to mild hyponatremia (130 to 135 mEq/L) or marked hyponatremia (< 130 mEq/

L) at baseline, the tolvaptan group showed a significantly greater increase in the average daily AUC for the serum Na⁺ concentration (*P* < 0.001). Within 8 hours after the first administration of tolvaptan, the serum Na⁺ concentrations were significantly higher in the tolvaptan group than in the placebo group for both the total patient population and the subgroups categorized to degree of hyponatremia at baseline (all *P* < 0.01). Significantly more patients in the tolvaptan-treated group had normal Na⁺ values at 30 days than placebo (*P* < 0.001). Urine output was significantly greater in the tolvaptan groups in both studies (*P* < 0.001). The most common adverse events were thirst and dry mouth, and other adverse events included dizziness, hypotension, acute renal failure, sepsis, and ascites. After discontinuation of treatment, patients' Na⁺ values decreased in both the tolvaptan and placebo groups and there was no statistical difference.

The long term use of tolvaptan in chronic hyponatremia was assessed in The Safety and sodium Assessment of Long-term Tolvaptan With hyponatremia: A year-long, open-label Trial to gain Experience under Real-world conditions (SALTWATER) study¹⁷). The SALTWATER study was an international, multicenter, nonrandomized, open-label extension of SALT-1 and -2 studies. In total, 111 patients with hyponatremia received oral tolvaptan for a mean follow-up of 701 days, providing 77,369 patient-days of exposure. Eligible patients had hyponatremia, finished SALT-1 and SALT-2 studies and wanted to continue tolvaptan therapy. Mean serum Na⁺ of patients increased from 130.8 mEq/L at baseline to more than 135 mEq/L during the study duration (*P* < 0.001). Serum Na⁺ in most patients of SIADH and heart failure was relatively well maintained at > 135 mEq/L compared to patients with liver cirrhosis. The most common adverse effects were pollakiuria, thirst, dry mouth, and polyuria. Six patients withdrew due to drug-related adverse effects including severe ventricular tachycardia, severe irritability, mild serum sodium increase, mild anorexia, severe azotemia, and moderate pruritus. Rapid correction of serum sodium (> 1 mEq/L/hr) occurred in 5 patients. Hyponatremia (> 145 mEq/L) was observed in one patient. This study showed that prolonged use of tolvaptan

could maintain increased serum Na^+ and also could have a modest safety margin in chronic hyponatremia.

The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) trials was 2 multicenter, randomized, double-blind, placebo-controlled studies that evaluated the effects of tolvaptan in patients hospitalized with heart failure (HF)¹⁸⁻²⁰. In total, 4,133 patients were enrolled and randomized to receive tolvaptan (30 mg/day) or placebo group, both groups were allowed the standard HF therapy, within 48 hours of admission. The mean follow-up time was 9.9 months. The withdrawal rate and adverse events (predominantly due to dry mouth and thirst) in both groups were similar. Rapid improvement of signs and symptoms was seen in the tolvaptan group without serious adverse events. However, there was no difference in the primary endpoints of all causes of mortality, the composite of cardiovascular death and HF hospitalization, or overall quality of life scores between the groups. Therefore, in HF patients, tolvaptan could not be initial standard therapy because of the evidence seen from EVEREST. Tolvaptan has not received approval from the United States Food and Drug Administration for this indication.

3. Indications, Dosing, and Administration

Tolvaptan is indicated for patients with clinically significant euvolemic or hypervolemic hyponatremia defined as $\text{Na}^+ < 125$ mEq/L and also indicated for mild hyponatremia ($\text{Na}^+ < 125$ – 135 mEq/L) in symptomatic patients, including patients with heart failure, cirrhosis, and SIADH that has resisted conventional therapy in the U.S.¹³. However, in the European Union (EU), tolvaptan is approved for use in adults with hyponatraemia secondary to SIADH. Tolvaptan should not be used in patients requiring intervention to rapidly correct serum Na^+ to prevent or treat neurologic symptoms. The initiation of tolvaptan should only occur in a hospital setting to allow for monitoring of the therapeutic response and to avoid rapid correction of hyponatremia. The usual initial dose of tolvaptan is 15 mg orally once daily without regard to meals. Dose adjustments can be made

after at least 24 hours, up to a maximum of 60 mg daily. Fluid restriction is not advised during the first 24 hours of therapy with the drug. Dosage adjustment according to age, gender, race, cardiac, mild-to-severe renal or hepatic function is not needed. Tolvaptan has not been evaluated in patients with a creatinine clearance 10 mL/min or in patients undergoing dialysis. However, no benefit can be expected in anuric patients¹³.

4. Contraindication and Precautions

Tolvaptan, in patients with a need to rapidly correct serum Na^+ , with an inability to sense thirst or appropriately respond to thirst, and hypovolemic hyponatremia, should be contraindicated¹³. Anuric patients have no clinical benefit of tolvaptan. The physician should take caution to avoid too rapid correction of serum Na^+ that may cause serious neurologic sequelae. Gastrointestinal bleeding more frequently occurs in liver cirrhosis patients receiving tolvaptan than in patients with placebo (10% vs. 2%)¹³. Common adverse events of tolvaptan, defined as a 5% greater incidence than placebo, were thirst, dry mouth, asthenia, constipation, and pollakiuria¹³.

5. Drug Interactions

Tolvaptan is metabolized via CYP3A4. While CYP3A4 inducers, such as rifampin, decrease plasma concentrations of tolvaptan by 85%, strong inhibitors of CYP3A4, such as ketoconazole, clarithromycin, cyclosporine, tacrolimus, fluoxetine, amiodarone, cimetidine, and midazolam, increase plasma concentrations¹³⁻¹⁵.

Conclusions

Through the SALT-1,-2, EVEREST, and SALTWATER studies, tolvaptan shows significant evidence that 1) it improves serum Na^+ levels patients with euvolemic or hypervolemic hyponatremia related with heart failure, cirrhosis or SIADH, 2) it has acceptable safety and tolerability for

long-term usage in chronic hyponatremia, and 3) the beneficial effects on serum Na⁺ occurred in patients with both mild and marked hyponatraemia. However, an initiation of tolvaptan treatment should be performed in the hospital setting because physicians must closely check the changes of serum Na⁺ during the dosage-titration phase. Tolvaptan, in Korea, is soon coming to the market. We hope that this article will assist in the understanding of tolvaptan and hope that this article may provide light on the subject.

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